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# Development and clinical trial of a smartphone-based colorimetric detection system for self-monitoring of blood glucose

HUNG-CHIH WANG,[1] FUH-YU CHANG,[1,*] TUNG-MENG TSAI,[2] CHIEH-HSIAO CHEN,[2,3] AND YEN-YU CHEN[2]

[1]Department of Mechanical Engineering, National Taiwan University of Science and Technology, Taiwan
[2]iXensor Co., Ltd, Taiwan
[3]China Medical University and Beigang Hospital, Taiwan
[*]fychang@mail.ntust.edu.tw

**Abstract:** Blood glucose measurements help to guide insulin therapy, thus reducing disease severities, secondary complications, and related mortalities. Efforts are underway to allow diabetes patients to experience a more convenient way to measure blood glucose and consequently increase their adherence to regular self-monitoring of blood glucose (SMBG). This study demonstrated a new SMBG system that integrated all components of a glucometer via a smartphone's optical sensing module to detect the colorimetric blood strip and obtains the blood glucose concentration with calculations performed by an application install in the smartphone. To validate the accuracy and applicability of the new SMBG system regarding the ISO15197:2013 accuracy criteria and patient requirements, a clinical trial and usability survey involving participants from different age groups were conducted in collaboration with the China Medical University, where enrolled 120 diabetic patients were asked to operate the new SMBG system to measure their blood glucose concentration, and feedback was obtained from their user experience. The results showed that three different reagent system lots fulfilled the accuracy requirements with values of 97.4–97.5% , and all of the data were within zones A and B of the consensus error grid, which satisfies the ISO 15197:2013 requirement. The usability survey showed that 97.5% of the participants found the operations convenient, and 100% found the design easy for carrying. This new system could lead to improvements in blood glucose monitoring by people with diabetes, and thus, better management of the disease.



## 1. Introduction

Obesity, sedentary lifestyles, increasing ages, and unhealthy diets have led to rapid growth in the diabetic population, which amounted to over 425 million people in 2017. This number is expected to continue to increase, with Cho et al. projecting that the number of people with diabetes will reach 629 million worldwide in 2045 [1]. Diabetes is a condition in which the blood sugar levels exceed the normal level. It occurs owing to either insulin deficiency or increased insulin resistance, which leads to high blood glucose [2,3]. Furthermore, it induces complications such as cardiovascular disorders, blindness, nephropathy, and limb amputation, ultimately leading to premature death of the patient [4]. Consequently, diabetes mellitus has become an important public health issue facing all countries in the world. Several researchers have pointed out that blood glucose levels can be effectively controlled through healthy diet, regular exercise, and frequent monitoring of blood glucose change, thereby reducing the incidence of complications from diabetes [5–11].

Accordingly, numerous glucose biosensors have been developed to assist diabetic patients with the self-monitoring of blood glucose (SMBG). These glucometers are based on interactions with one of three enzymes: hexokinase, glucose oxidase (GOx), or glucose dehydrogenase

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(GDH) [12]. Among them, most SMBG glucometers are based on the GOx enzyme, because such measurements are cheap and easy to obtain, and the devices are durable against extremes of pH, ionic strength and temperature, and show relatively higher selectivity for glucose than many other enzymes [13,14]. The signal transducers of glucose biosensors have been widely analyzed using various electrochemical and optical methods. Electrochemical biosensors operate by measuring the reaction current or electric charge after the glucose in the blood reacts with the enzyme in the test paper, and converting the measured value into blood glucose concentration [15–17]. Optical biosensors are based on colorimetry. In these biosensors, blood glucose test strips with special enzymes are used to produce chemical reactions with blood glucose and changes in the glucose concentration are monitored by the reflected wavelength that is detected, which is then converted into blood glucose concentration [18–22]. However, current glucometer components include a meter, test strips, a lancing device, lancets, and alcohol swabs, which makes the glucometer bulky. Consequently, the glucometer is inconvenient to carry, and this approach requires multi-operation steps to obtain the blood glucose values. This reduces the willingness of patients to detect their blood glucose level frequently, and inaccurate measurement data on blood glucose levels will likely lead to the injection of incorrect insulin dosages, which can cause excessively high or low blood glucose. This could seriously impact the health of diabetic patients, even endangering their lives [23]. To avoid the risk of inaccurate glucometer readings, the International Organization for Standardization (ISO) published a new standard, ISO 15197:2013, in 2013. This standard defines the minimum acceptable accuracy for a glucose monitoring system [24]. Recent studies have reported that differences in test strips, vials of test strips, and lots of test strips will cause deviations in inspection results because small variations in the reaction well size and/or loss of enzyme coverage during manufacture processing may influence the accuracy of blood glucose systems as well as reduce mediator concentration [25–27]. To avoid the situation, ISO 15197:2013 prescribes the use of three different test strip lots to evaluate the accuracy of blood glucose systems. Measurement results are analyzed using the consensus error grid (CEG), in which 99% of the results should fall within zones A and B [28].

This study presents a colorimetric glucometer system that combines a designed integrated detection device for blood glucose (IDDBG) with a smartphone to measure blood glucose using automatic glucose concentration analysis software. The most important feature of the IDDBG, which is designed without any electronic parts. It does not require any extra light source during the detection of blood glucose concentrations. In addition, the IDDBG has a minimal feature size, thus enabling high portability, and it can be easily installed over the smartphone camera. In this experiment, a clinical trial was performed with three different lots of IDDBG to verify whether the developed SMBG system meets the ISO 15197:2013 accuracy criteria. For this purpose, blood glucose levels of diabetes mellitus patients were measured by using the IDDBG system with a smartphone and a standard biochemical blood glucose analyzer. These measured data were compared and analyzed to confirm the accuracy and precision of the new SMBG system. Finally, a usability survey was conducted to assess whether the smartphone-based IDDBG system is easy to operate and convenient to carry and whether there are other issues that need to be addressed. The survey results can be used as the basis for improvements in the next stage.

## 2. Experiment methods

### 2.1. Design and optical light tracking simulation

In this study, the IDDBG was designed as a portable and small device with dimensions of L:35 mm × W:20mm × H:9.1mm; the major components are an isolated ambient light enclosure, a colorimetric test strip (CTS), a reflector channel, a disposable blood lancet, and alignment plate, as shown in Fig. 1(a). In this concept, the CTS image is captured with the camera module of the smartphone using the smartphone's LCD screen as a light source. At first, the computer-aided design (CAD) software was used to build the IDDBG 3D model, and then an optical light

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tracking simulation was performed using Tracepro (Lambda Research Corporation) to determine the optimal design for the IDDBG, as shown in Fig. 1(b). The optimal height and reflector angle (RA) of the reflector channel for reflecting light into the CTS area were determined to achieve optimized illuminance and illumination uniformity on the CTS area. In this simulation experiment, the height was set from 4 mm to 7 mm with 1 mm intervals and RA was set from 30° to 70° with 5° intervals as the analysis conditions. In this manner, the relationship between the height and RA to illumination could be analyzed and the most optimal height and RA of the reflector channel for the best illuminance on the observation area of the CTS could be determined. The actual illumination of the smartphone's LCD (230 lux) measured using the T10 illuminance meter (Konica Minolta, Japan) was set as the light source illuminance value in the simulation. According to this measurement, the light source area was set to be 7.5 mm × 6.3 mm in the simulation. The light wavelength was set by the general colorimetric method, in which the 550 nm wavelength is the most commonly used. The number of simulated traces was set to be 3 million. In a previous study, the nine-point uniformity method was used to analyze and achieve optimized illuminance and illumination uniformity on the CTS area [29].

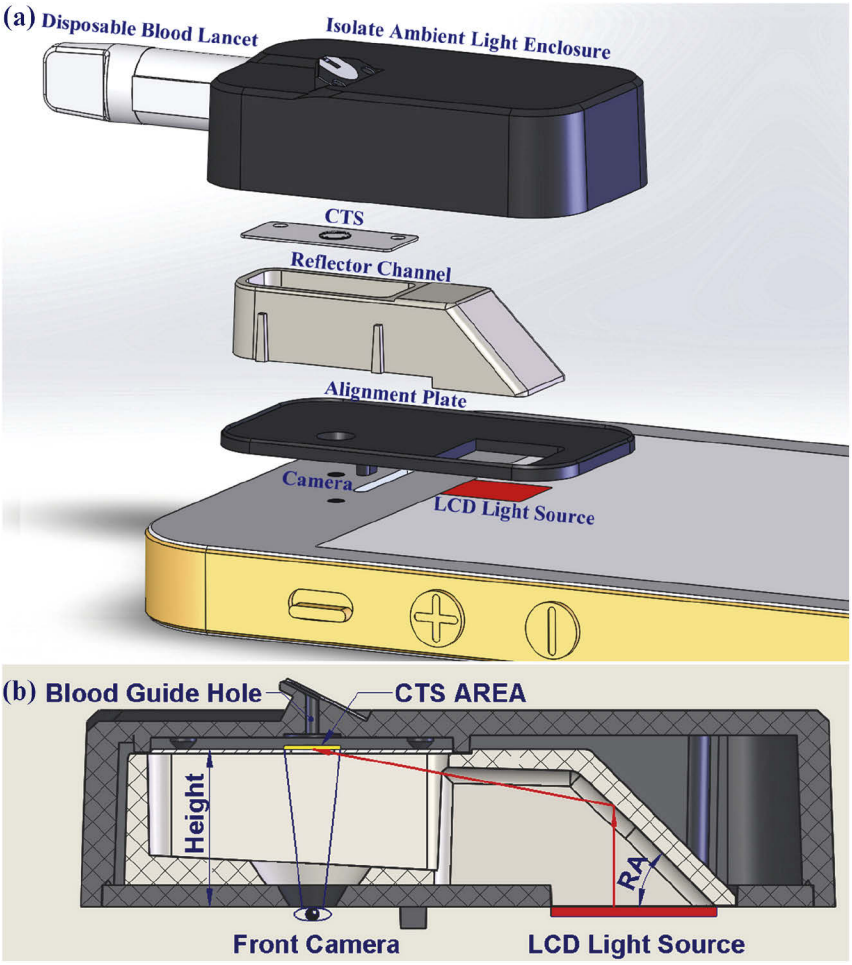


**Fig. 1.** (a). Smartphone and IDDBG, comprising the isolated ambient light enclosure, CTS, reflector channel, alignment plate, and disposable blood lancet. (b). Optical light tracking simulation structure. The red arrows indicate the light path in the IDDBG.

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### 2.2. Optical light tracking simulation result

First of all, the relationship between the height and angle to illumination on the CTS observation area was analyzed. The illumination at reflector channel height of 4 mm and RA of 30° was 22.0 lux, while that at RA of 50° was 22.7 lux, representing the minimum and maximum illumination, respectively. The difference between the maximum and minimum is 0.7 lux and the average value is 22.5 lux. As the height was increased, illuminance continuously increased. At 7 mm, the average illuminance reached the highest value at 53.0 lux. At this height, the maximum and minimum values of illumination were 53.7 lux and 50.4 lux at RAs of 50° and 30° , respectively. The difference between the maximum and minimum illumination was 3.3 lux. The best illuminance uniformity (95.5%) was achieved under the condition of 7 mm height and the 50° RA. The height and RA results for illuminance and illuminance uniformity are shown in Fig. 2. According to the simulation, the height of 7 mm and RA of 50° were selected in the final design of the light guide channel to achieve the optimal illuminance and illumination uniformity.

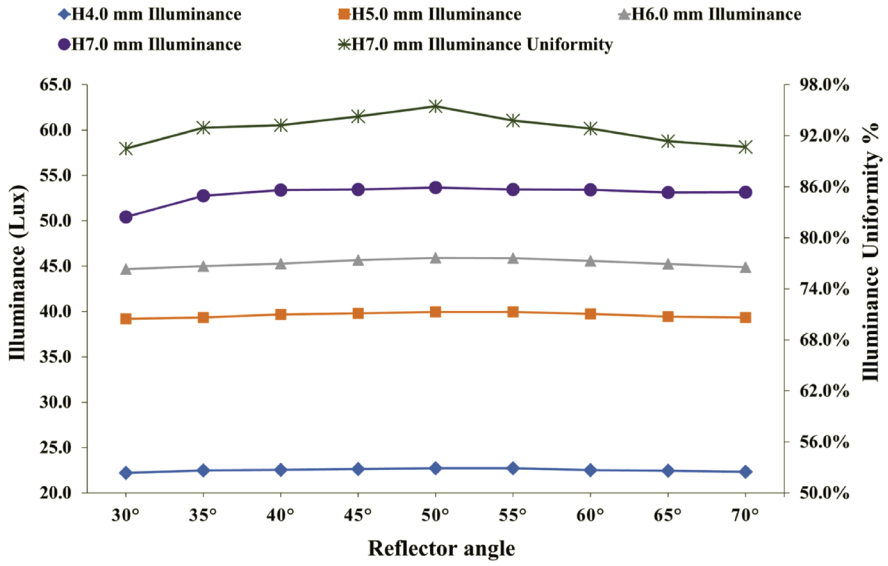


**Fig. 2.** Simulation results of illuminance and illuminance uniformity on the CTS.

### 2.3. Fabrication of IDDBG components

Except for the CTS, all the IDDBG components were fabricated via plastic injection molding in this study. This method allows the fabrication of components with consistent characteristics at a reasonable production cost. To avoid contamination of these components by oil or dust, all components were cleaned with ultrasonic cleaning and then assembled together. The injection mold was fabricated by the CNC machine center, and the reflector surface was polished by the precision polishing machine with a 3000 grid diamond buff in the reflective area to ensure the surface roughness of a mirror and enhance the light reflection efficiency of the reflector channel. The surface roughness can obtain Ra 0.025 to 0.05 $\mu$ m. General marketed products of colorimetric blood glucose strips (BSI Visual Glucose Strip, Biomedical System International Inc.) with concentrations of 40–500 mg/dL were selected as the CTS material, and a cutting tool was used to cut the strips to a size of 7.5 mm × 6.3mm in accordance with the IDDBG standard.

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### 2.4. Collection of whole blood samples and establishment of the signal reference mainline

Blood samples taken from vein vessels are called whole blood samples, which include the major components of plasma, red blood cells, white blood cells, and platelets [30,31]. Whole blood has special fluid viscosity different from that of general glucose standard liquids. To ensure the accuracy of the experiment, whole blood was collected to test the characteristics of the general colorimetric glucose strip, and establish a reference mainline for blood glucose concentration in this study. However, collecting blood samples with different glucose concentrations for experimental purposes is difficult. Moreover, whole blood glucose has a special characteristic in that it degrades to 0 mg/dL after standing for more than 24 h at the ambient temperature of 22°C [32]. Considering this issue, sterile heparin tubes were used to collect 120 cc whole blood samples from blood donation, which were then allowed to stand for 24 h. Afterward, a Yellow Springs Instrument biochemical blood glucose analyzer equipment (YSI-2300, USA) was used to verify whether the blood glucose concentration degraded to 0 mg/dL. Proper amounts of glucose solutions were added to samples without blood glucose according to the required blood glucose concentration. Subsequently, a YSI-2300 was used to measure the whole blood glucose concentration.

In practice, each type of colorimetric enzyme strips has their own specific color, sensitivity, and time required for clearly distinguishing the blood glucose concentration value. To determine the feature of each colorimetric enzyme strip and establish the signal reference mainline, 10 different blood glucose concentrations from 50 mg/dL to 500 mg/dL were set with an interval of 50 mg/dL and the accuracy of the concentration measured using the YSI-2300 equipment was validated. After inserting the CTS into the IDDBG, changes occurred in the brightness and color of the CTS area for different glucose concentrations. At this time, the system detected the brightness change of the CTS area with the light sensor of the smartphone, and activated the front camera of the smartphone to capture the CTS's color image change (iPhone 5s, Apple Inc., USA). Then, the RGB signal of CTS's image were separated with the ColorAssist program (FTLapps. Inc.). Through the experiment, 10 different concentration curves of RGB signals were obtained with the normalized algorithm and the determined signal was used to establish linear equations with the linear regression analysis method. Normalization was performed by dividing the reaction signal value by the non-reaction signal. Given that the normalized signal values for each concentration were too low so as to easily distinguish them, the range of the normalized signal values for each concentration was rescaled up to 400 times, as shown in Eq.(1). The non-reaction signal means an initial RGB signal of the colorimetric test strip. The methods facilitate easy acquisition of specific RGB signals and the time required to clearly distinguish on the colorimetric enzyme strips. Finally, a linear equation was applied as the signal reference mainline with the primary objective of converting the color change for different concentrations on the CTS to blood glucose concentration values. Because this experiment involved three lots of IDDBG for each of which the IDDBG was separately fabricated, three different reference mainlines were considered. Each lot of IDDBG was marked to easily identify their corresponding reference mainlines. In this study, an automatic glucose concentration analysis software (AGCAS) that captures the RGB signal data of the CTS reaction and compares it with the signal reference mainline was developed. Subsequently, a blood glucose concentration value could be obtained.

$$N = \frac{S'}{S} X400\,, \tag{1}$$

Where $N$ is the 400 times rescale of the normalization RGB signal value, $S$ is the none-reaction RGB signal value, and $S'$ is the reaction RGB signal value.

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### 2.5. Clinical trial plan for verifying the developed SMBG system

In this study, the performance of the IDDBG with a smartphone monitoring system was verified through a clinical trial at the China Medical University Hospital. The main objective was to focus on numerical accuracy and verify whether it meets the stringent accuracy acceptance criteria of ISO 15197:2013 section 6.3. The accuracy criteria define: (1) 95% of measurement results must fall within ± 15 mg/dL of the reference measured glucose concentration <100 mg/dL or within ± 15% of the reference measured glucose concentration ≥ 100 mg/dL (2) 99% of the results shall fall within zones A and B of the consensus error grid (CEG). [24]

#### 2.5.1. Clinical trial design

The design of a survey with the involvement of human subjects was approved by the China Medical University Hospital and informed consent was obtained from the subjects. For the clinical trial, there were three lots of IDDBG in this study. In selecting subjects, diabetic patients who met the following criteria were considered for inclusion in the study: type 1 or type 2 diabetes, age 20 years or older, hematocrit (HCT) value within 35% ~ 55%, and willingness to complete all study procedures. Individuals with the following conditions or characteristics were excluded from the study: 1. Intake of prescription anticoagulants (such as Warfarin or Heparin), except for daily intake of Plavix or aspirin, or clotting problems that may prolong bleeding. 2. Hemophilia or any other bleeding disorder, or records of infection caused by blood-borne pathogens (e.g., HIV, hepatitis). 3. Hematocrit value not within 35% ~ 55%. Finally, 120 subjects were selected for the trial. The subjects used the IDDBG with the smartphone system to measure blood glucose, and the accuracy of the measurement results was assessed via comparisons to the YSI-2300 glucose analysis values.

#### 2.5.2. Clinical trial process

To ensure that the subjects satisfied the requirements of clinical practice and to assist them to successfully complete the test, the clinical procedure was divided into the following three parts: first, pre-test documentation review and patient qualification confirmation; second, an introduction and description of the IDDBG operating procedures; third, a satisfaction survey of usability. Each part of the clinical trial is described in detail below.

**Pre-clinical documentation review and patient qualification confirmation process** 1. Potential subjects are pre-screened for inclusion into the study by using the inclusion/exclusion form (I/E Form). Each subject completes the I/E Form in the presence of a technician, and the physician excludes patients with hemophilia or any other bleeding disorder.

2. Following confirmation that each subject met the requirement, the confidentiality agreement form was executed and the medical history form completed.

3. Each subject was assigned a subject number starting with 0001 followed by consecutive numbers, such as 0002.

**Introduction and description of the IDDBG with smartphone operating procedures** Each subject was escorted to the testing area and provided with the IDDBG operation process instructions, which included seven steps, as shown in Fig. 3.

Step 1: Before testing, wash your hands using warm, soapy water, and then rinse and dry them completely.

Step 2: Turn on the smartphone and open the AGCAS app.(see Fig. 3(a)).

Step 3: Pick the IDDBG and twist the protective cap on the disposable blood lancet clockwise twice and put it away (see Fig. 3(b)).

Step 4: Put the IDDBG on the smartphone's LCD screen. (see Fig. 3(c))

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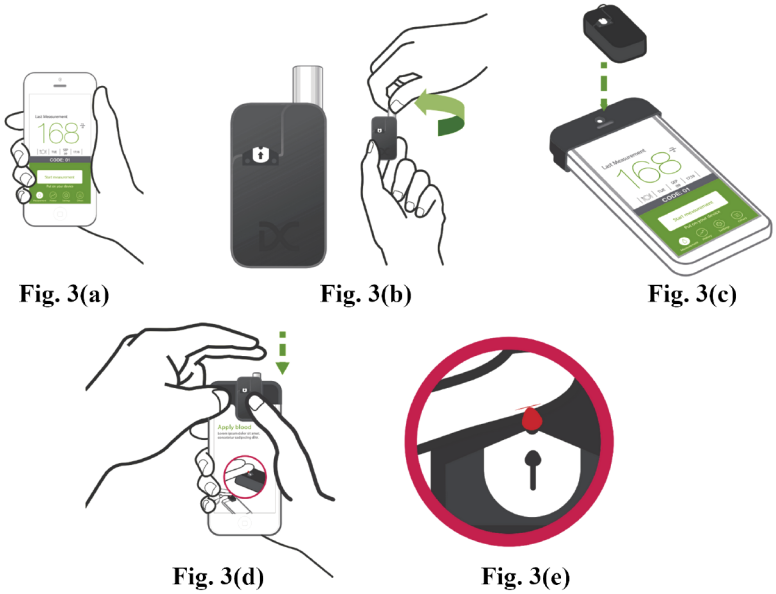


**Fig. 3.** Operation procedures for IDDBG with a smartphone to measure blood glucose concentration.

Step 5: To obtain the blood glucose sample, hold the disposable blood lancet firmly against you finger to prick it (Fig.3(d)).

Step 6: Place the drop of blood in the blood guide hole of the IDDBG (Fig. 3(e)).

Step 7: Read/Note/Record your blood glucose concentration as it appears on the smartphone LCD screen.

Once the subject gains confidence in their abilities to perform the required steps (i.e., strip placement, blood application, and reading the display screen), they were requested to demonstrate these tasks to a member of the trial staff. After successful demonstration of these tasks, the subjects were allowed to proceed to the next steps. A member of the trial staff recorded the ability of the subjects to demonstrate these tasks. When the subjects finished the blood glucose measurement process, the smartphone's LCD screen displayed the blood glucose values and these values were recorded. Meanwhile, a YSI-2300 glucose analysis was used to confirm the blood glucose level. The staff recorded the data on the glucose test results-subject (GTR). The HCT value was checked with the standard machine (BECKMEN LX20) used in the hospital, and the results were recorded on a test result form, which was then verified by a trained technician.

### 2.5.3. Usability and user experience surveys

After completing the blood glucose measurement procedure, a survey of each subject's overall operational convenience and portability was conducted. The survey analyzed whether the success rate of IDDBG operations will cause operational distress considering each age group. Finally, an interview was conducted to understand the subjects' perception of the designed concept of the actual operation of the IDDBG with a smartphone. Divided into operability convenience and portability convenience for the survey, the subjects could select from the following four options: excellent, good, not good, and bad. According to the survey results, a determination was made as to whether the design concept of IDDBG satisfies the study requirement.

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## 3. Results and discussion

### 3.1. Selection of the RGB signal and reference mainline

The developed SMBG system was applied to record RGB signal values every 0.2 s for 50 s, and each concentration sample was measured three times. The normalized algorithm was applied and 10 different concentration curves of RGB were obtained. In this experiment, G signal was selected as a reference mainline as it can clearly identify different concentration of the blood glucose value of the sample after 10 seconds [29]. Subsequently, the parametric regression analysis method was used to obtain three linear equations of the three lots. These linear equations as shown in Eq(2), (3), (4), and Fig. 4. The three linear equations were used as the signal reference mainline in the automatic glucose concentration analysis software (AGCAS), which was used to convert the imaged strip colors to the blood glucose concentration for three different lots of IDDBG. In this study, the lot number of the signal reference mainline was printed on the CTS to prevent the diabetes patients choosing the wrong lot number to measure their blood glucose with the new SMBG system. Three lots of signal reference mainlines were saved in the AGCAS. The new SMBG system can identify the lot number symbol on the CTS with the smartphone's camera to select the correct lot number. In the future, lots of the colorimetric test strip will be produced, and the lot numbers of the new versions of the signal reference mainlines data will be uploaded to the cloud database. The new SMBG system will then detect the cloud database through the internet, and then the new version of the signal reference mainlines can be downloaded from the App Store.

$$y = -0.3415x + 213.82\,, \tag{2}$$

$$y' = -0.3215x + 223.53\,, \tag{3}$$

$$y'' = 0.3315x + 218.68\,, \tag{4}$$

Where $y$, $y'$, and $y''$ are the linear equations of Lot1, Lot2, and Lot3, respectively

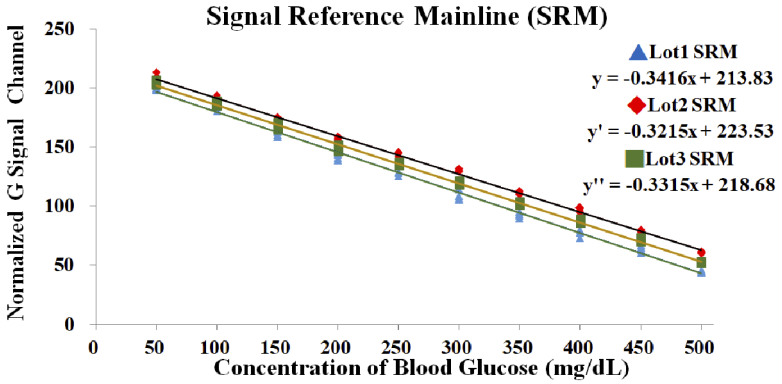


**Fig. 4.** Three lots of linear equations as signal reference mainline that obtained based on the normalized value of the G signal with the linear regression analysis method. The linear equation is used to correlated signal to concentration. Glucose concentrations of 50~500 mg/dL were recorded with the IDDBG and G signal and the results were read with a smartphone.

### 3.2. Clinical trial result for the developed SMBG system

Of the 120 subjects involved in the clinical trial, 28 were type 1 diabetes patients and 92 were type 2 diabetes patients. Regarding the age distribution, 1.7% of the subjects were under the age of 20, 6.7% were within 21– 30, 20.8% were within 31– 40, 30.8% were within 51– 60, 23.3%

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were within 61– 70, and 5% were over the age of 71, as shown in Fig. 5. We further analyzed the data for the 120 diabetes patients that measured data from only 118 subjects were used because two patients unfamiliar with the operation of the new SMBG system, and their tests could not be completed. The difference plot analysis of the 118 diabetes samples allowed us to compare the measured results from the developed SMBG system to the measured results from the YSI-2300 glucose analyzer, and the relative bias according to Bland and Altman was also ascertained [33]. The analysis of the data shown that 115 diabetes patients fell within the ± 15 mg/dL or ± 15% criteria. The percentages of three strip lots within the accuracy limits were 97.4% (Lot 1), 97.5% (Lot 2), and 97.4% (Lot 3), as shown in Fig. 6(a). And the bias analysis results of these three strips lots were -2.11% (Lot 1), -1.98% (Lot 2), and -2.24% (Lot 3), respectively. After investigating the three blood samples which did not meet the ± 15% criteria, the failure could be attributed to the insufficient blood supplied by the patients on the strips when measuring their blood glucose. Meanwhile, the CEG analysis for the test strips of different lots showed that two samples fell within zone B, the other samples fell within zone A. Therefore, 100% of the various strip lots results fell within the zones A and B of CEG, as shown in Fig. 6(b). The accuracy of the new SMBG system satisfied the ISO15197:2013 criteria. Because hypoglycemia is very dangerous for diabetic patients, an accuracy below 100 mg/dL is therefore critical. This clinical trial had only eight subject's blood glucose below 100 mg/dL. Even the results show that all of the data fell within the ISO 15197:2013 accuracy criteria. However, below 100 mg/dL diabetes patient subjects are not enough, which is a weakness of this clinical trial. In the next phase clinical trial, the number of diabetes patients with different blood glucose should be enrolled in an evenly distributed manner.

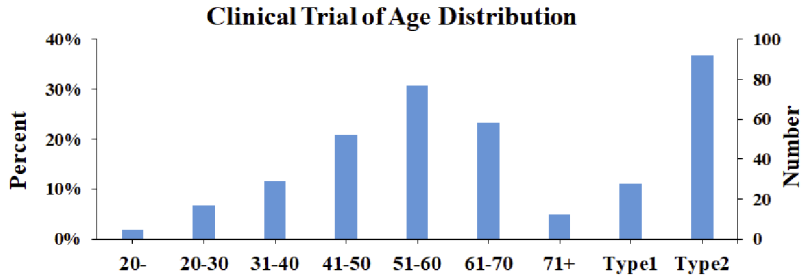


**Fig. 5.** Participant age survey results. Among 120 subjects, 28 were type1 diabetes patients and 92 were type 2 diabetes patients. Further, 1.7% were under the age of 20, 6.7% were 21 to 30, 20.8% were 31 to 40, 30.8% were 51 to 60, 23.3% were 61 to 70, and 5% were over 71.

### *3.3. Usability and user experience surveys results*

All the subjects were able to complete the operation and measure blood sugar successfully by the end of the experiments. The usability survey revealed that 97.5% of the subjects found the IDDBG very convenient for use. The remaining 2.5% of the subjects found the IDDBG inconvenient as they do not use smartphones frequently; these subjects were within the age group of 61– 71, as shown in Fig. 7(a). All of the subjects felt that the IDDBG combined with the blood glucose strip and disposable lancet were easy to carry, thus confirming the portable design, as shown in Fig. 7(b). Regarding the usability survey, 2.5% of the subjects who found the IDDBG inconvenient mentioned that the operation procedure was not easy to follow in terms of placing the finger into the blood guide hole, even with the indication of the hole location. In addition, 7.7% of the satisfied subjects also mentioned this problem, although they could complete the process. Considering the age distribution, most of the subjects who responded to this problem were over 61 years of age. The problem can be thus attributed to their diabetic condition and old

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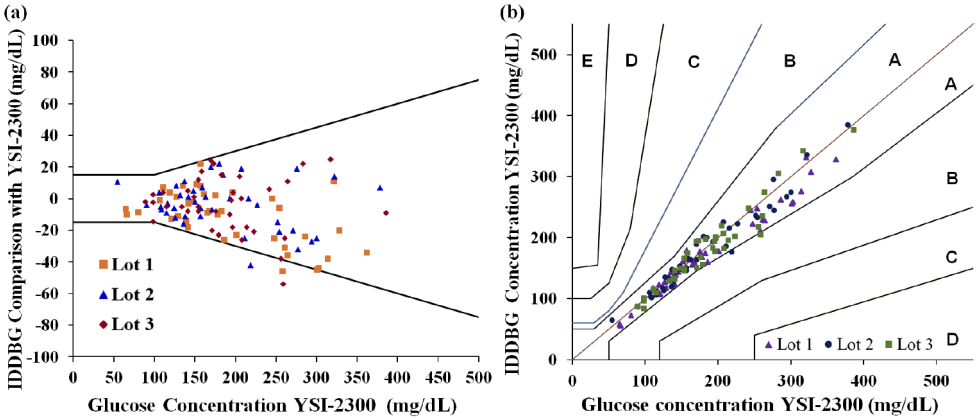


**Fig. 6.** Difference plot and consensus error grid analysis results. (a) Comparison of the measured data from the developed SMBG system and from the YSI-2300 analyzer for 118 diabetes patient's specimens. Solid lines indicate system accuracy limits of ISO 15197:2013. The results showed that each of three lots of strips has one sample out of the accuracy criteria. Therefore, the percentages of three lots of strips trial results within the accuracy limits were 97.4%(Lot 1), 97.5% (Lot 2), and 97.4% (Lot 3). (b) For the consensus error grid (CEG) analysis results showed that 2 samples fell within zones B (would not lead to inappropriate treatment), and 116 samples fell within zones A (indicates no effect on clinical action). Therefore, 100% of the various strip lots' results fell within the zones A & B.

age, which contributed to their poor vision. Meanwhile, 5% of the subjects responded that they experienced obvious pain when using the disposable blood lancet to draw blood, although it was not a significant inconvenience. To address the two problems identified from the feedback of the subjects, the following improvements will be implemented. The blood guide hole structure can be redesigned to more clearly indicate the hole location such that diabetic patients can easily place the blood in the CTS area. Meanwhile, to reduce the feeling of pain, the diameter and penetration depth of the needle can be reduced.

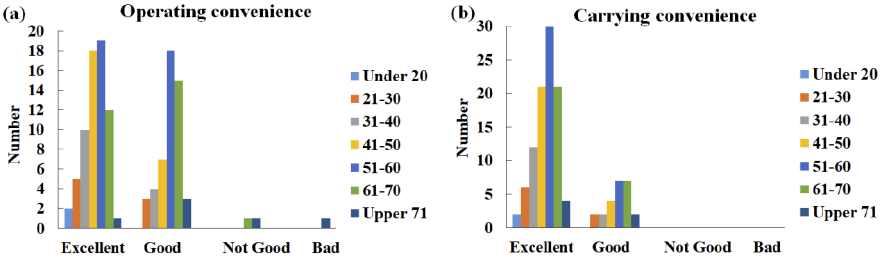


**Fig. 7.** Usability survey results for the operation and carrying convenience. (a) 97.5% of the subjects felt that the IDDBG is convenient to operate. (b) 100% of the subjects felt that the IDDBG is convenient to carry.

## 4. Conclusions

This study demonstrates the convenient use and portability of a self-monitoring blood glucose system comprising an integrated detection device of blood glucose and a smartphone. The innovative aspects of the IDDBG with a smartphone can be summarized as follows. (i) It uses the smartphone screen light as the light source for taking images and does not require an additional

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light source. (ii) It is as small as a pen cap and does not include any electronic parts or require an external power supply. An optical ray-tracing simulation was performed to determine the best reflection conditions in the IDDBG, and optimal and uniform illumination on the IDDBG colorimetric blood strip area could be achieved by using a smartphone LCD screen as the light source. A clinical trial and usability survey involving participants from different age groups were conducted in collaboration to confirm the accuracy and applicability of the new SMBG system. The results showed that three different reagent system lots fulfilled the accuracy requirements with values of 97.4–97.5%, and all three strip lots were within CEG zones A and B, which satisfies the ISO15197:2013 requirements. The usability survey showed that 97.5% of the participants found the operations convenient, and 100% found the design easy for carrying. The use of smartphones for analyzing images is a growing research trend. According to the technology principle of this study, our future plan is to develop a personal health management system that can detect cholesterol, glycated hemoglobin (HbA1C), triglycerides, and even provide semi-quantitative luteinizing hormone ovulation test results to help women make better fertility plans. Then, the measured data can be integrated into a personal health management program and analyzed, and this information can be provided to relevant medical staff for pharmaceutical and therapeutic reference. Through this personal health management system, personal physiological information can be controlled and recorded more effectively with the aim of ensuring a healthy life.

## Abbreviations

SMBG: self-monitoring blood glucose; CEG: consensus error grid; GDH: glucose dehydrogenase; GOx: glucose oxidase; ISO: International Organization for Standard; IDDBG: integrated detection device for blood glucose; CTS: colorimetric test strip; CAD: computer-aided design; RA: reflector angle; HCT: hematocrit; HIV: human immunodeficiency virus; I/E Form: Inclusion/Exclusion Form; GTR: glucose test results-subject; AGCAS: automatic glucose concentration analysis software; HbA1C: glycated hemoglobin; CNC:computer numerical control;

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## Disclosures

T.M.Tsai, C.H.Chen, and Y.Y.Chen are cofounders of iXensor Co., Ltd., and H.C.Wang was an employee of iXensor Co., Ltd. F.Y.Chang has no relevant conflict of interests to declare.

## References

1. N. Cho, J. Shaw, S. Karuranga, Y. Huang, J. D. da Rocha Fernandes, A. Ohlrogge, and B. Malanda, "IDF Diabetes Atlas: Global estimates of diabetes prevalence for 2017 and projections for 2045," Diabetes Res. Clin. Pract. **138**, 271–281 (2018).
2. D. G. Gardner and D. Shoback, *Greenspan's Basic & Clinical Endocrinology* (McGraw-Hill Medical, 2011).
3. "About Diabetes," World Health Organization. Archived from the original on 31 March 2014. Retrieved 4 April 2014. (2014).
4. "Diabetes Fact sheet N°312," WHO. October 2013. Archived from the original on 26 August 2013. Retrieved 25 March 2014. (2011).
5. N. Poolsup, N. Suksomboon, and S. Rattanasookchit, "Meta-analysis of the benefits of self-monitoring of blood glucose on glycemic control in type 2 diabetes patients: an update," Diabetes Technol. Ther. **11**(12), 775–784 (2009).

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6. S. Skeie, G. B. Kristensen, S. Carlsen, and S. Sandberg, "Self-monitoring of blood glucose in type 1 diabetes patients with insufficient metabolic control: focused self-monitoring of blood glucose intervention can lower glycated hemoglobin A1C," J. Diabetes Sci. Technol. **3**(1), 83–88 (2009).
7. S. L. Tunis and M. E. Minshall, "Self-monitoring of blood glucose (SMBG) for type 2 diabetes patients treated with oral anti-diabetes drugs and with a recent history of monitoring: cost-effectiveness in the US," Curr. Med. Res. Opin. **26**(1), 151–162 (2010).
8. E. I. Boutati and S. A. Raptis, "Self-monitoring of blood glucose as part of the integral care of type 2 diabetes," Diabetes Care **32**(suppl_2), S205–S210 (2009).
9. L. Jovanovic, "Using meal-based self-monitoring of blood glucose as a tool to improve outcomes in pregnancy complicated by diabetes," Endocr. Pract. **14**(2), 239–247 (2008).
10. M. J. O'Kane and J. Pickup, "Self-monitoring of blood glucose in diabetes: is it worth it?" Ann. Clin. Biochem. **46**(4), 273–282 (2009).
11. R. Weiss and I. Lazar, "The need for continuous blood glucose monitoring in the intensive care unit," J. Diabetes Sci. Technol. **1**(3), 412–414 (2007).
12. C. P. Price, "Point-of-care testing in diabetes mellitus," Clin. Chem. Lab. Med. **41**(9), 1213–1219 (2003).
13. A. Heller and B. Feldman, "Electrochemical glucose sensors and their applications in diabetes management," Chem. Rev. **108**(7), 2482–2505 (2008).
14. S. B. Bankar, M. V. Bule, R. S. Singhal, and L. Ananthanarayan, "Glucose oxidase–an overview," Biotechnol. Adv. **27**(4), 489–501 (2009).
15. D. Grieshaber, R. MacKenzie, J. Vörös, and E. Reimhult, "Electrochemical biosensors-sensor principles and architectures," Sensors **8**(3), 1400–1458 (2008).
16. C. Shan, H. Yang, J. Song, D. Han, A. Ivaska, and L. Niu, "Direct electrochemistry of glucose oxidase and biosensing for glucose based on graphene," Anal. Chem. **81**(6), 2378–2382 (2009).
17. X. Kang, J. Wang, H. Wu, I. A. Aksay, J. Liu, and Y. Lin, "Glucose oxidase–graphene–chitosan modified electrode for direct electrochemistry and glucose sensing," Biosens. Bioelectron. **25**(4), 901–905 (2009).
18. A. Koh, D. Kang, Y. Xue, S. Lee, R. M. Pielak, J. Kim, T. Hwang, S. Min, A. Banks, P. Bastien, M. Manco, L. Wang, K. Ammann, K.-I. Jang, P. Won, S. Han, R. Ghaffari, U. Paik, M. Slepian, G. Balooch, Y. Huang, and J. Rogers, "A soft, wearable microfluidic device for the capture, storage, and colorimetric sensing of sweat," Sci. Transl. Med. **8**(366), 366ra165 (2016).
19. B.-H. Hou, H. Takanaga, G. Grossmann, L.-Q. Chen, X.-Q. Qu, A. M. Jones, S. Lalonde, O. Schweissgut, W. Wiechert, and W. B. Frommer, "Optical sensors for monitoring dynamic changes of intracellular metabolite levels in mammalian cells," Nat. Protoc. **6**(11), 1818–1833 (2011).
20. A. J. Haes and R. P. Van Duyne, "A nanoscale optical biosensor: sensitivity and selectivity of an approach based on the localized surface plasmon resonance spectroscopy of triangular silver nanoparticles," J. Am. Chem. Soc. **124**(35), 10596–10604 (2002).
21. X.-D. Wang, T.-Y. Zhou, X. Chen, K.-Y. Wong, and X.-R. Wang, "An optical biosensor for the rapid determination of glucose in human serum," Sens. Actuators, B **129**(2), 866–873 (2008).
22. G. Chang, Y. Tatsu, T. Goto, H. Imaishi, and K. Morigaki, "Glucose concentration determination based on silica sol–gel encapsulated glucose oxidase optical biosensor arrays," Talanta **83**(1), 61–65 (2010).
23. C. H. Raine III, L. E. Schrock, S. V. Edelman, S. R. D. Mudaliar, W. Zhong, L. J. Proud, and J. L. Parkes, "Significant insulin dose errors may occur if blood glucose results are obtained from miscoded meters," J. Diabetes Sci. Technol. **1**(2), 205–210 (2007).
24. International Organization for Standardization, "ISO 15197:2013. In vitro diagnostic test systems – Requirements for blood-glucose monitoring systems for self-testing in managing diabetes mellitus," (2013).
25. M. Erbach, G. Freckmann, R. Hinzmann, B. Kulzer, R. Ziegler, L. Heinemann, and O. Schnell, "Interferences and limitations in blood glucose self-testing: an overview of the current knowledge," J. Diabetes Sci. Technol. **10**(5), 1161–1168 (2016).
26. A. Baumstark, S. Pleus, C. Schmid, M. Link, C. Haug, and G. Freckmann, "Lot-to-lot variability of test strips and accuracy assessment of systems for self-monitoring of blood glucose according to ISO 15197," J. Diabetes Sci. Technol. **6**(5), 1076–1086 (2012).
27. B. H. Ginsberg, "Factors affecting blood glucose monitoring: sources of errors in measurement," J. Diabetes Sci. Technol. **3**(4), 903–913 (2009).
28. G. Freckmann, M. Link, C. Schmid, S. Pleus, A. Baumstark, and C. Haug, "System accuracy evaluation of different blood glucose monitoring systems following ISO 15197: 2013 by using two different comparison methods," Diabetes Technol. Ther. **17**(9), 635–648 (2015).
29. H.-C. Wang, F.-Y. Chang, T.-M. Tsai, C.-H. Chen, and Y.-Y. Chen, "Design, fabrication, and feasibility analysis of a colorimetric detection system with a smartphone for self-monitoring blood glucose," J. Biomed. Opt. **24**(02), 1 (2019).
30. A. Farley, C. Hendry, and E. McLafferty, "Blood components," Nurs. Stand. **27**(9), 35–39 (2012).
31. H. Popp, "Blood Banking and Transfusion Medicine: Basic Principles & Practice," Pathology **35**(5), 457 (2003).
32. L. M. Mikesh and D. E. Bruns, "Stabilization of glucose in blood specimens: mechanism of delay in fluoride inhibition of glycolysis," Clin. Chem. (Washington, DC, U. S.) **54**(5), 930–932 (2008).
33. J. M. Bland and D. Altman, "Statistical methods for assessing agreement between two methods of clinical measurement," Lancet **327**(8476), 307–310 (1986).